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Introduction, General Findings and General Recommendations*

Objectives

The Workshop/Conference, the deliberations of which are reported here, has sought to assess the present state of knowledge in metal carcinogenicity as the basis for seeking unifying principles and making recommendations for research needed to fill gaps in our present understanding of metal carcinogenicity relevant to public health.

Although the ultimate aim of the recommendations put forward concerns knowledge which will be applicable to the prevention of human cancer, it is recognized that this requires an understanding of the mechanisms of action ranging from the molecular level to organ response, as well as methods for the epidemiological study of human disease. Accordingly, the Workshop/Conference brought together a multidisciplinary group in order to undertake a conceptually linked examination of the progression of tumors from their initiation to malignancy. In this examination, specific attention was given to the role of potential interaction with other agents.

Attention has also been given to predictive testing for carcinogenic metallic compounds by both whole animal and *in vitro* methods.

Although the Workshop was not charged with a formal evaluation as to whether a specific metallic compound is or is not carcinogenic, as, for example, in the IARC Monographs, it was felt that the data at hand made it possible to reach conclusions for a number of the metals. In addition, the Workshop took as one of its major objectives the development of recommendations to improve our understanding of metal carcinogenicity. There has been no attempt to review safety standards for human exposure or techniques involving quantitative extrapolation to man from high to low doses whether based on human data or laboratory tests. On the other hand, the qualitative meaning of laboratory tests for man, both short-term and long-term, has been examined.

Historical Review

The chronology of observations of the carcinogenicity of some metallic compounds is illustrated in Figure 1. In most but not all instances, a clinical report of a cluster of cancer cases was the signal for subsequent epidemiologic and animal studies. Thus, cancer from arsenic was reported in 1888 (*1*) in a group of persons treated with Fowler's solution. The first systematic epidemiologic study was not undertaken until 1948 (*2*). Despite many attempts to reproduce cancer in animals with arsenic compounds, failure has been the rule. Recently, however, suggestive evidence of carcinogenicity in rats was reported. They were dosed with a Bordeaux mixture containing arsenic (*3*).

It may be noted that in the earlier instances (Fig. 1) the first suspicion came from case reports. In two more recent cases, the first signal came from animal studies (Fig. 1). As for beryllium and cadmium, the most reasonable interpretation of available data is that compounds of these metals have contributed to the development of lung cancer in the case of beryllium and prostatic cancer in the case of cadmium in exposed workers.

In general, systematic epidemiologic investigation is required to validate an association of one or several possible etiologic factors. Normally such studies are weak in, or even incapable of, identifying specific causal agents. At this level, animal studies are of particular value; it may be that *in vitro* tests can increasingly aid in such identification.

Workgroup I recognized the prudence of the approach taken by IARC in suggesting that substances for which there is sufficient evidence of

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carcinogenicity in animal studies should be regarded as if they were carcinogenic in man.

Importance of Metals in Carcinogenesis

Of about 80 metals there are at least 20 which have compounds that have been reported to give rise to well-defined toxic effects in man. Only a few of these metals have been shown or are suspected to be carcinogenic. The importance of metal carcinogenesis does not so much concern the number of carcinogenic compounds, but rather the ubiquity of exposure, their wide industrial use, and their persistence in the environment. Thus, implementation of appropriate protective measures for metallic compounds proven to be carcinogenic may be difficult in comparison with organic carcinogens which are likely to be less persistent. Thus, arsenic (a recognized carcinogen) is found to occur in high concentrations in drinking water in some parts of the world. In these areas, skin cancer has been associated with the drinking of such water. Only drastic measures will reduce the exposure substantially.

In industry, exposure is often not to a single metal only, but instead to mixtures. Significant amounts of a large number of metals have been found at autopsy in the lungs of workers with a high risk for lung cancer who retired from their work in a smelter several years before their death. The difficulties in evaluating causal relationships are obvious; in such instances the interactions must be considered. Furthermore, whenever a metal is classified as carcinogenic or noncarcinogenic, such a statement should only apply to specific forms of the metal. There is ample evidence that metabolism, toxicity in general, and also carcinogenicity are dependent on the chemical and physical forms of a metal.

Metal compounds may cause alteration or interfere with a number of intracellular biochemical mechanisms and may also induce toxic effects not related to carcinogenesis. Some metals, e.g., lead, exert toxic effects on the nervous system, which, at the present, determine accepted exposure levels to a large extent. On the other hand, other metals, e.g., Cr(VI) and Ni compounds, induce predominantly carcinogenic effects. In evaluation of health risk and in setting priorities for epidemiological and experimental cancer studies, these considerations should be taken into account.

Methods of Evaluation

Epidemiological Studies

Epidemiological studies identify the incidence of cancer in groups of humans who experience different environmental conditions. If different groups

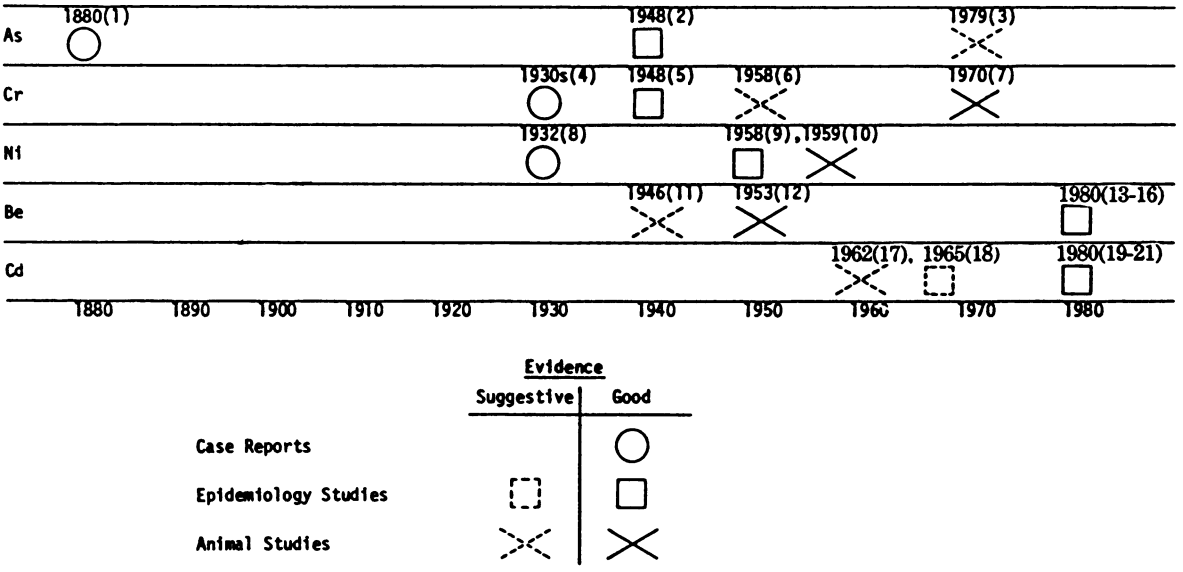

FIGURE 1. Chronology of observations on the carcinogenicity of metallic compounds judged by this workshop as contributing to human cancer. The suspected metallic compounds are not specified in the figure but listed as the element. As pointed out elsewhere, however, specific metallic compounds are usually the carcinogenic entity and not the element as such. References are shown in parentheses.

are exposed to different amounts of a carcinogenic agent, it may be possible to determine the relationship between the amount of exposure and the resulting cancer incidence and thence to make quantitative estimates of the risk involved. Because the studies are always carried out in real life situations, it is seldom, if ever, possible to design them in such a way as to satisfy the strict requirements of experimental design that are normal in the laboratory; and there may be some doubt about the interpretation that should be attached to their results. Nevertheless, epidemiological studies have the overwhelming advantage that they refer directly to humans and they provide the only certain means for designating a metal compound as a human carcinogen.

Clinical case reports have served as useful warning signals of the existence of risk on a number of occasions in the past, and they may still do so occasionally in the future. It ought to be possible, however, to organize the collection of observations on humans in such a way that any risks that have inadvertently been caused are picked up more quickly and more certainly by planned inquiry. One form of inquiry is the case-control study. Such studies have proved valuable in establishing the reality of a risk, but the method that is most generally applicable to the detection of occupational hazards is the cohort study, in which groups of exposed workers are followed up to determine their experience of disease. The problems involved in using cohort studies to obtain evidence about the carcinogenic effect of metals on humans, or the lack of any such effect, are discussed in the introduction to the report of Workgroup IB.

Whole Animal Experiments

Several *in vivo* experimental models have been used to evaluate the potential carcinogenicity of pure metals or some of their inorganic and organic compounds and to investigate the factors modifying their activity.

Several endpoints may be considered, such as the development of a tumor at the site of contact or at a distance in the treated animals or their offspring (transplacental carcinogenesis) and chromosomal damage in germinal or somatic cells. The last two types of effects (transplacental carcinogenesis and chromosomal aberrations) have rarely been looked for in animals treated with metallic compounds.

One important advantage of animal experiments is the fact that the chemical and physical properties of the administered metallic compounds can be well defined. The investigation of the carcinogenic potential of well characterized complex mixtures, the comparison of the carcinogenic potency by various routes, and different compounds of the same metal administered is possible. Animal studies simulating the usual route of human exposure may be particularly useful in an evaluation of the physical and chemical forms most hazardous for humans. For example, animal studies have shown that the most active chromium compounds for the development of lung cancer are the hexavalent salts of intermediate solubility.

Those animal studies which use routes of administration different from those by which man is usually exposed have limitations for extrapolating the results to man; nevertheless, such studies may provide useful information on internal factors (absorption, distribution, immunological status, etc.) and external factors (e.g., interaction with other metallic compounds or organic chemicals) influencing the carcinogenic or cocarcinogenic potency of metallic compounds. For example, it has been demonstrated that the combined injection of Mn and Ni_3S_2 reduced the numbers of local sarcomas relative to IM injection of Ni_3S_2 alone.

Unfortunately, whole animal carcinogenesis studies with metals and their compounds are still very limited. Data on species variation and dose-response relationships are lacking for the majority of metals. One important disadvantage of animal experiments is that they can be time and space consuming. In some cases whole animal models are less useful than *in vitro* systems for investigating the molecular mechanisms of action of carcinogens.

In Vitro Mutation Test Systems

In vitro bacterial mutation test systems have proven highly useful for studying a number of metational mechanisms involving direct effects of metals on DNA metabolism. Alteration of DNA structure, infidelity of DNA synthesis, and excision repair processes have all been reported following *in vitro* incubation with metals of carcinogenic concern. Studies using metals with mammalian cells *in vitro* have demonstrated in some instances increased viral or morphologic transformation of some cell lines following incubation with a number of metals. One potential problem with such tests is the fact that at present each system measures only those types of mutational events to which it is specifically sensitive and, hence, comparative studies of different mutational mechanisms in one system are lacking. Another area of concern involves the question as to what extent the mutational mechanisms observed in these test systems may be expected to operate in normal mammalian cells *in vivo*. The degree to which potentially toxic metals

are sequestered from direct interaction with DNA *in vivo* by binding to high affinity intracellular ligands or traps is also presently unknown.

Other studies involving effects of metals on subcellular systems of essential importance to cellular viability or metabolism of organic carcinogens showed that these systems were also highly susceptible to metal toxicity.

Potential ramifications of these observations are that metals may act as promoters of the carcinogenic response by stimulating cell turnover and/or altering cellular susceptibility to organic carcinogens or their metabolic derivatives. The effects of metal alteration of microsomal or S_9 fraction on activation of *in vitro* mutation test systems are also presently unknown. Studies of metal effects on subcellular systems which metabolize organic carcinogens are also currently largely lacking and hence the potential cocarcinogenic effects of these metals on the carcinogenic response from organic carcinogens are unknown.

General Findings and Recommendations

General Finding 1

There exists a serious lack of quantitative data that can be used for dose-response evaluations on occupational exposure to potentially carcinogenic metal compounds.

Recommendations

Monitoring programs should be planned and implemented to measure exposures in the work environment. In addition to measurements of total exposure levels to metal compounds, means should be sought to develop and apply procedures for the characterization of the biologically important physical and chemical characteristics of metal compounds in the work environment. Whenever appropriate, possible cocarcinogenic agents should also be measured.

Assessment of exposure to suspected metal compounds in workroom air should take into account intake by: (1) inhalation, including, where practicable, estimated mucociliary transport with subsequent ingestion, (2) direct ingestion, e.g., direct contact with fingers, cigarettes, etc., or (3) skin contact.

Where possible, exposure to suspected metal compounds should be estimated through analysis of biological samples of blood, urine, saliva, hair and feces, and autopsy specimens.

General Finding 2

For several potentially carcinogenic metal compounds there are also inadequate data on exposure levels of the general population.

Recommendations

Monitoring programs should be planned to estimate exposure of the general population to carcinogenic metals. Due attention should be given to all routes of exposure and to measurement through biological monitoring and measurement in biopsy and autopsy specimens wherever feasible.

In instances of probable exposure of the general population to compounds of carcinogenic concern, identification of specific chemical species, in addition to the total metal concentration, should be undertaken.

General Finding 3

Several reports indicate gross analytical errors of importance for evaluation of exposure to metals.

Recommendation

Internationally accepted analytical methods and standard reference material should be developed for measurements of carcinogenic metals in environmental and biological samples. These can serve for validation of routine analytical procedures. International programs for analytical harmonization should be promoted, and reference materials should be made available.

General Finding 4

Environmental exposure to carcinogenic metals results generally in cancer in a small fraction of exposed individuals. This indicates that factors determining the susceptibility to cancer induction play a decisive role.

Recommendation

Effort should be made to identify factors determining susceptibility and to identify susceptible groups.

General Finding 5

For both occupationally exposed groups and the general population very few studies are available on the relationship between tissue concentration of the carcinogenic metal compound and the carcinogenic

response. Data are also lacking for experimental animals.

Recommendation

Concentrations of metals or, whenever possible, their suspected active species should be measured in biological samples (blood, urine, biopsy or autopsy material) from exposed populations and experimental animals in order to detect possible correlations between such concentrations and effects in terms of precancerous lesions or fully developed carcinogenic effects. Such studies would also aid in reaching quantitative estimates of relationships between tissue concentrations and carcinogenic response.

General Finding 6

Metals are elements and, as such, they have been an intrinsic component of the environment to which man is adapted. Specific compounds of some metals are required for human life, and some metals are thus designated "essential metals."

With several metals a distinct possibility exists that metals essential at one level or route of intake might be carcinogenic at another level or route. At different levels it is necessary to consider changes in chemical speciation and whether or not the levels exceed the capacity of the normal homeostatic mechanisms.

Recommendation

Systematic investigations are necessary to identify the carcinogenic chemical species or, for the same chemical species, the role of the physical state—particle size and surface properties, as well as concentration. Attention should be given to their biochemical interconversions in solution and biotransformations, and to compare these forms with their nutritionally essential states. These investigations should be explored on a quantitative basis.

General Finding 7

It has been suggested that chromosomal aberrations, sister chromatid exchange, and DNA repair are of predictive value in relation to cancer development.

Recommendation

Further studies should be conducted at the epidemiological and laboratory levels to evaluate the reliability of these approaches.

General Finding 8

There are examples of biological interactions involving metals that lead to alteration of tumor response, e.g., dietary zinc intake in laboratory animals or a number of organic carcinogens. Also, exposure situations are often complex. In environments which have been demonstrated to cause an excess risk of cancer, a number of possible interactions may be operating (e.g., SO_2–arsenic interactions in smelter environments).

Recommendation

Possible enhancing or inhibitory effects of exposure to various metal compounds in combination with other carcinogens or cocarcinogenic compounds should be examined in appropriate animal, cellular, *in vitro*, and epidemiological studies. The mechanisms by which metals cause such effects should be elucidated.

General Finding 9

Lifetime studies in animals have been found to be predictive of probable carcinogenicity in man, especially when the routes of exposure and the sites of the tumors are the same. However, a positive outcome, even with different routes of exposure or differences in the tumor site, yields suggestive evidence of possible carcinogenicity for man.

Recommendation

When used for predictive testing, whole animal studies should, as a rule, employ a similar route of exposure as the one encountered in humans. Other routes of administration may be usefully employed especially in the investigation of mechanisms of action.

General Finding 10

Negative epidemiological studies should be evaluated in the same way as positive studies and their results taken fully into account when assessing the human evidence. The acquisition of sufficient and adequate date with which to evaluate the carcinogenicity or lack of carcinogenicity of metals in humans requires a study period at least comparable to the induction time for carcinogenesis.

Recommendation

Negative epidemiological studies of adequate duration should be published and the confidence limits of risk estimates included when relevant.

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